DIFFERENCES IN EFFICACY OF INTERACTION OF DIALKYLAMINOALKYL AND DIALKYLAMINOACYL DERIVATIVES OF PHENOTHIAZINE WITH MEMBRANE RECEPTORS

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The membranotropic action of many drugs is complex and includes both the basic mechanisms of action on the cell membrane and also other, less marked effects. We know, for instance, that the pharmacologic effect of neuroleptics is exerted through the blockade of dopamine receptors (DR) of the brain, but many of them are also antagonists of histamine receptors (HR), α-adrenergic (AR), and muscarinic receptors (MR) [10]. On the other hand many antiarrhythmic drugs have not only a direct depressive action on transmembrane ionic currents, but also block receptors of hormones and neurotransmitters [2]. Phenothiazine derivatives with marked cardiotropic properties, and without any neuroleptic action, have been synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. These include the antiarrhythmic agents ethmozine (ETM) and ethacizine (ETC), recently introduced into clinical practice, and also the antianginal agent nonachlazine. In their chemical structure these preparations are 10-N-dialkylaminoacyl derivatives of phenothiazine.

Comparative analysis of binding of the new compounds with membrane receptors and binding of preparations of phenothiazine nature already known is of both practical and theoretical interest, for the study of dependence of the pharmacologic effect on chemical structure of the drug opens the way ahead to the oriented synthesis of drugs.

In this investigation we used three dialkylaminoacyl derivatives, namely G-512, G-219, and G-229, which are structural analogs of dialkylaminoalkyl derivatives [chlorpromazine (CP), trifluoperazine (TFP), and fluphenazine (FP) respectively] and also ETM and ETC. We determined their affinity for D_2R of the bovine striatum, α_1 and α_2-AR, M_1R and H_1R of the rabbit cerebral cortex, and M_2R and β_1-AR of the rabbit heart.

EXPERIMENTAL METHOD

Membranes were isolated from the bovine striatum and ^{3}H-spiperone binding carried out by the method in [11]. Membranes of the rabbit cerebral cortex were isolated by the method in [12]. Binding of ^{3}H-prazosin and ^{3}H-clonidine was carried out by the method in [4], and of ^{3}H-pirenzepine as in [13], and ^{3}H-pirilamine as in [4]. Isolation of the membranes from the ventricles of the rabbit heart and binding of ^{3}H-quinuclidinyl-benzylate (^{3}H-QNB) were carried out by the method in [13] and binding of ^{3}H-dihydroalprenolol by the method in [91. Solutions of the preparations were made up immediately before the experiments, which were done in two parallel series, using 7-12 concentrations of the test preparations. Inhibition constants were calculated by the formula of Cheung and Prussoff [5].

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TABLE 1. Interaction of Phenothiazine Derivatives with Membrane Receptors

Substance	^{3}H-spiperone	Inhibition constant, μM				
		^{3}H-prazosin	^{3}H-clonidine	^{3}H-pirenzepine	^{3}H-QNB	^{3}H-pirilamine
CP	0,015	0,0015	5	0,101	0,38	0,007*
G-512	5,2	1,5	15	0,0042	0,048	4,4
G-219	0,007	0,009	10	0,7	100	0,051*
TFP	3,8	5,5	7,3	1,3	10	7,0
G-229	10,005	0,012	1,5	1,1	100	0,027*
ETC	12	1,5	15,3	1,2	10	4,2
ETM	—	13,0	55,0	0,7	0,7	7,0
	—	26,0	40,0	3,0	222,0	11,0

Legend. Asterisk marks results taken from [10]. Concentrations of radioligands in incubation medium are similar to their dissociation constants. Nonspecific binding did not exceed 45%.

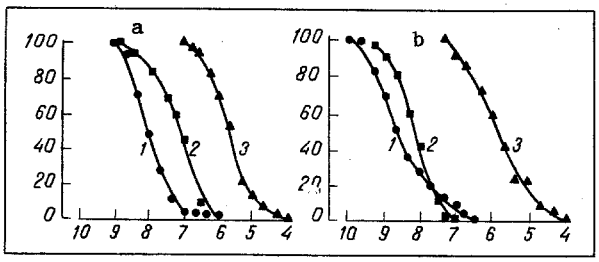

Fig. 1. Typical concentration dependence of binding of preparations with M_2R (a) of rabbit heart and M_1R (b) of rabbit brain. Abscissa, log of concentration of preparation (in M); ordinate, binding of ^{3}H-QNB (a) and ^{3}H-pirenzepine (b) with M_2R and M_1R respectively (in %). 1) Atropine, 2) G-512, 3) ETC. Each experimental point was tested in three parallel experiments.

EXPERIMENTAL RESULTS

All the results, presented in the form of mean values of two or three independent experiments, are given in Table 1. They show that all the dialkylaminoacyl derivatives are significantly less able than neuroleptics to interact with central D_2, α_1-AR, and H_1R. It can be tentatively suggested that because of the low affinity of the new derivatives for these receptors, they ought not to induce any marked central effects such as are characteristic of neuroleptics. This is in agreement with data demonstrating that ETM and ETC have virtually no effect on the dopamine-sensitive adenylate cyclase system of the brain [1] and have no neurleptic action.

In experiments to study displacement of ^{3}H-clonidine, an α_2AR agonist, no differences were found in the affinity of the two groups of preparations. Both types of α-AR are distributed in the cardiovascular system of all species of mammals, and their activation leads to effects such as vasoconstriction, platelet aggregation, inhibition of noradrenalin secretion, a positive inotropic effect, etc. [8]. The ability of the compounds tested to interact with α-AR in micromolar concentrations may be important in the case of their peripheral action. We know, for example, that in the clinical use of certain neuroleptics of phenothiazine nature α-adrenoblocking effects are observed (bradycardia, vasodilatation) [7].

None of these preparations was effective against β_1-AR of the rabbit heart in concentrations up to 100 μM inclusive.

Interesting results were obtained in the experiments with MR. All compounds except ETC showed selectivity toward M_1R. The strongest affinity for these receptors, similar to atropine, was found with compound G-512 (Fig. 1). It is evident that in this case substitution of the radical in the 10-N-position for the acyl radical of CP leads to increased affinity for M_1R. This compound also proved to be highly effective in its interaction with M_2R (Fig. 1b). However, it was less effective against this type of MR than atropine, but to both M_1R and M_2R it had greater affinity than ETC, the inhibition constant of which coincides with the effective therapeutic dose (150-200 mg/day). Analysis of the displacement curves between Hill's coordinates [6] shows that the test substances interact with receptors with coefficients close to 1, i.e., by a mechanism characteristic of interaction

between antagonists and receptors. The stronger cholinolytic activity of ETC than of ETM may be one reason for the difference in their pharmacologic properties. It is possible that the atropinelike action of ETC makes its own contribution to the use of this drug in arrhythmias associated with a disturbance of sinus node activity [3].

The results show that replacement of the alkyl radical in position 10 by an acyl radical considerably reduces the affinity of the compounds for D_2R, α_1-AR, and H_1R. In the case of CP this substitution also leads to potentiation of its cholinolytic properties. Similarity of the chemical structure of the test preparations and of their spectra of action on membrane receptors with those of ethacizine and ethmozine suggests that the spectrum of their pharmacologic action may also be closely similar.

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